

Crossing the Species Barrier — One Small Step to Man, One Giant Leap to Mankind

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On first setting foot on the moon, Neil Armstrong famously proclaimed that he had taken “One small step for man, one giant leap for mankind.” With minor adjustments, he could have been referring to one of the most important distinctions between limited outbreaks of infectious diseases and the occurrence of devastating pandemics: one small step to man, one giant leap to mankind. Recent events, such as the reports of cases of avian influenza and monkeypox in humans and the outbreak of severe acute respiratory syndrome (SARS), bring this distinction into sharp focus.

Many infectious diseases cross the species barrier. Generally, this crossing occurs either because humans come into contact with a microorganism that is already capable of causing human infection or because an alteration occurs in the spectrum of species for which the organism is pathogenic — the so-called host range. The majority of these infectious agents are zoonotic, meaning that their usual host is a nonhuman vertebrate. In some cases, the assignment of a “usual” host is rather arbitrary, since the pathogen may be found in many different species. The bacteria that causes Lyme disease, *Borrelia burgdorferi*, and rabies virus are examples of zoonotic pathogens that have a broad host range. These pathogens, along with many others, intermittently enter the human population as a result of contact between humans and an already competent pathogen. In the case of Lyme disease, human contact occurs through the bite of an insect vector, the tick carrying the bacteria, that usually resides harmlessly in white-footed mice or deer. In the case of rabies, direct contact between humans and an infected vertebrate animal is the usual mode of transmission. Similarly, the recently described cases of monkeypox and tanapox infections in humans resulted from direct contact with infected prairie dogs and chimpanzees, respectively. In each of these cases, molecular evidence suggests that the genome of the mi-

croorganism is virtually the same whether the organism is isolated from the animal or the infected human. Epidemiologic links to direct contact with infected poultry have been implicated in almost all the cases of human infection with avian influenza A, which expresses the H5 type hemagglutinin and the N1 type neuraminidase. And detailed sequence analysis of the isolates of avian influenza A (H5N1) virus from patients in Vietnam reveals that it is unchanged from the isolates from infected poultry, as shown by polymerase chain reaction in the report by Hien et al. in this issue of the *Journal* (see pages 1179–1188).

The outbreak of SARS coronavirus (SARS-CoV) infections in humans represents something partway between a small step to man and the feared giant leap to mankind. There is strong evidence that this coronavirus was present in a population of animals in China, including the Himalayan palm civet (*Paguma larvata*). Through molecular changes, most likely in its spike glycoprotein, SARS-CoV broadened its host range in such a way that it became capable of attaching to human cells and infecting humans who were directly exposed to these animals. Seroprevalence studies involving persons who sold these animals for consumption in China demonstrated that antibodies to the new SARS-CoV developed in more than 70 percent of the animal handlers. Thus, under the right circumstances, the transmission from animals to humans was relatively efficient.

But SARS-CoV had an additional feature: it could be spread not only from animals to humans, but also from one human to another — albeit inefficiently. It is important to emphasize the efficiency of human-to-human transmission. Although there are rare instances of human-to-human transmission of infectious diseases whose transmission usually requires direct contact with animals — for example, rabies, which has been transmitted from human to human under extraordinary circumstances,

such as corneal transplantation from an infected tissue donor — SARS-CoV crossed the species barrier to humans and then was transmitted from clinically ill persons to household contacts, health care workers, and even passengers who were seated near the ill persons on airplane flights. However, from recent seroprevalence studies, we have learned that very few people who had direct contact with patients with confirmed SARS-CoV infection actually became infected.

The epidemiologic significance of the transmission of infectious agents from animals to humans depends on such factors as the density of the infected animal hosts (e.g., poultry), the frequency with which susceptible humans come into contact with these animals, and the biology of the pathogen, including its mode of transmission and the efficiency of its spread from human to human. Thus, in Asia, where there remain large numbers of poultry that are infected with the influenza A (H5N1) virus and are in contact with humans, even if interspecies transmission is rare, we can anticipate additional cases in humans.

The giant leap to mankind that leads to pandemic infections requires the introduction into the non-immune human population of a microorganism that is not only infectious but also efficiently transmitted from person to person. When such an organism is introduced, each new case results in multiple new human infections. How does a pathogen step across the species barrier so that it becomes capable of efficient person-to-person transmission?

Genetic-exchange events appear to be particularly important. First, we must think of such potential pathogens (especially viruses) not as single, fixed species but as dynamic populations of numerous variants that undergo selective pressure. When different microbial populations can coexist in multiple susceptible mammalian hosts, there is an increased likelihood of mixing of genetic material in recombination events. We are only beginning to understand the molecular mechanisms underlying the selection process and, ultimately, the change in the efficiency of transmission.

In the 1918 influenza pandemic, influenza A (H1N1) infected more than 20 million people worldwide in the largest recorded outbreak of any

infectious disease. Although no intact influenzavirus exists from that pandemic, some insights have been gained from fragments of the virus that were isolated from archived autopsy specimens and from the tissue of Alaskan natives that was preserved in permafrost. A key event appears to have been caused by a recombination in the hemagglutinin gene that resulted in a novel virus with increased virulence. Although it is not clear exactly where or in what species the recombination event among these viral populations occurred, the apparent parental strains of the pandemic avian influenzavirus were capable of infecting mammals, including swine and humans. The reassortment of genes between human and avian strains apparently also caused the 1957 pandemic of Asian influenza (H2N2) and the 1968 pandemic of Hong Kong influenza (H3N2).

As we consider a future in which we must be concerned about emerging infectious diseases, it is imperative that we augment existing public health and research capabilities. The global and domestic monitoring of infectious diseases by agencies such as the World Health Organization and the Centers for Disease Control and Prevention has been remarkably successful in accomplishing the rapid identification of emerging pathogens and their epidemiologic description. Enhanced capacity for worldwide collaborative monitoring and a larger public health workforce, including persons with expertise in veterinary public health, that can implement containment measures are essential. What is especially needed is a coordinated effort to study the pathogenesis of emerging infectious diseases and to use this information for the rapid development of therapeutic agents and vaccines. The network of research laboratories funded by the National Institutes of Health for the study of emerging and reemerging infectious diseases represents an important investment for filling this void. Although emerging infectious diseases such as the avian influenzavirus will continue to take small steps across the species barrier, the prize will be the avoidance of giant leaps to mankind.

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